Original article

Comparative evaluation of the efficacy and safety of two doses of terbinafine (500 and 1000 mg day^{-1}) in the treatment of cutaneous or lymphocutaneous sporotrichosis

Vergleichende Bewertung der Wirksamkeit und Sicherheit zweier Terbinafin-Dosierungen (500 und 1000 mg/Tag) in der Therapie der kutanen und lymphokutanen Sporotrichose

S. W. Chapman,[1] P. Pappas,[2] C. Kauffmann,[3] E. B. Smith,[4] R. Dietze,[5] N. Tiraboschi-Foss,[6] A. Restrepo,[7] A. B. Bustamante,[8] C. Opper,[2,9] S. Emady-Azar[10] and R. Bakshi[10]

[1]University of Mississippi Medical Center, Jackson, MS, USA, [2]University of Alabama, Birmingham, AL, USA, [3]University of Michigan Medical School and Veteran Affairs Medical Centre, Ann Arbour, MI, USA, [4]University of New Mexico, Albuquerque, NM, USA, [5]Núcleo de Doenças Infecciosas, Universidade Ferderal do Espirito Santo, Vitoria, Brazil, [6]University of São Paulo, Ribeirão Preto, São Paulo, Brazil, [7]National University of Columbia, Medellin, Columbia, [8]Instituto de Medicina Tropical 'Alexander von Humboldt', Universidad Peruana Cayetano Heredia, Lima, Peru, [9]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA and [10]Novartis Pharma AG, Basel, Switzerland

Summary

The aim of this study was to evaluate the safety and efficacy of oral terbinafine (500 and 1000 mg day^{-1}) in the treatment of cutaneous or lymphocutaneous sporotrichosis. A culture for *Sporothrix schenckii* was required for inclusion into this multicentre, randomized, double-blind, parallel-group study. Patients received either 250 mg b.i.d. or 500 mg b.i.d. oral terbinafine for up to a maximum of 24 weeks and were assessed up to 24 weeks post-treatment. The main efficacy outcome measure was cure, defined as no lesion and absence of adenopathy at the end of follow-up. Adverse events (AEs), laboratory tests, vital signs and ophthalmological examinations were also assessed. Sixty-three patients (14–85 years of age) were treated with 500 mg day^{-1} ($n = 28$) or 1000 mg day^{-1} terbinafine ($n = 35$). The majority of patients were cured after 12–24 weeks of treatment, and the response was dose-dependent throughout the study and at the end of follow-up. The cure rate was significantly higher in patients treated with 1000 mg day^{-1} terbinafine compared with those treated with 500 mg day^{-1} terbinafine (87% vs. 52%, respectively; $P = 0.004$). There were no cases of relapse after 24 weeks of follow-up in the 1000 mg day^{-1} terbinafine group, compared with six relapses in the terbinafine 500 mg day^{-1} group. Terbinafine was well tolerated and the frequency of drug-related AEs was slightly higher in the 1000 mg treatment group. Both doses of terbinafine were well-tolerated and effective for the treatment of sporotrichosis. The 1000 mg day^{-1} terbinafine dose was more efficacious than 500 mg day^{-1} in the treatment of cutaneous or lymphocutaneous sporotrichosis.

Correspondence: Dr Rajesh Bakshi, Novartis Pharma, CH 4002, Basel, Switzerland.
Tel.: +41-61-3243075. Fax: +41-61-3244984.
E-mail: rajesh.bakshi@pharma.novartis.com

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Zusammenfassung

Ziel der Studie war die Sicherheit und Wirksamkeit der oralen Terbinafin-Therapie (500 und 1000 mg/Tag) in der Behandlung der kutanen und lymphokutanen Sporotrichose zu prüfen. In die Studie wurden 63 Patienten im Alter von 13 bis 85 Jahren aufgenommen, die entweder mit 500 mg/Tag (n = 28) oder 1000 mg Terbinafin/Tag (n = 35) behandelt wurden. Bei allen Patienten wurde Sporothrix schenkii durch Kultur nachgewiesen. Die Heilungsrate war signifikant höher in der 1000 mg Gruppe, in der während 24 Wochen Nachkontrolle kein Rückfall beobachtet wurde. Im Gegensatz hierzu traten in der 500 mg Gruppe 6 Rezidive auf. Terbinafin wurde gut toleriert; die Häufigkeit der Nebenwirkungen war in der 1000 mg-Gruppe leicht erhöht. Beide Terbinafin-Dosierungen als gut verträglich und wirksam. In der Behandlung der kutanen und lymphokutanen Sporotrichose war die 1000 mg-Terbinafin-Dosierung jedoch wirksamer als die 500 mg-Dosis.

Key words: Sporotrichosis, lymphocutaneous infection, antimycotic chemotherapy, terbinafine, efficacy.

Schlüsselwörter: Sporotrichose, lymphokutane Infektion, antimykotische Chemotherapie, Terbinafin, Wirksamkeit.

Introduction

The dimorphic fungus, *Sporothrix schenckii* naturally exists saprophytically and has a worldwide distribution. Sporotrichosis is caused by the traumatic implantation of this fungus into the skin from contact with soil, plant debris, thorns, sphagnum moss or timber.[1,2] The infection may remain confined to the inoculation site (fixed cutaneous), presenting as a small, painless, erythematous papule that may ulcerate or become verrucous.[3]

In many cases (70–80%) the infection spreads by lymphatic drainage to form a series of nodules along the lymphatic vessels (lymphocutaneous).[3,4] Thus, secondary lesions develop proximally, yet these are often painless and may eventually drain and ulcerate.[3,4] In addition, sporotrichosis can disseminate and present with pulmonary or systemic involvement, but this is rare, except in immunocompromized patients.

In otherwise healthy people, the most common forms of sporotrichosis are not usually life-threatening, but these conditions do not resolve spontaneously and treatment is necessary. A saturated solution of potassium iodide (SSKI) has been used for treating sporotrichosis for approximately 100 years, although its mechanism of action is unclear.[5,6] SSKI is still recommended, but new agents with more convenient dosing regimens and lower frequencies of adverse events (AEs) are needed.[7] The azole antifungals, especially itraconazole, have also proved effective in the treatment of lymphocutaneous sporotrichosis.[7]

Terbinafine is a synthetic allylamine derivative that has long-term effectiveness in the treatment of superficial dermatophyte infections and onychomycosis.[8,9] However, the therapeutic potential of terbinafine may extend beyond its current uses. *In vitro* studies have suggested that terbinafine exhibits potent activity against a broad spectrum of pathogenic fungi that are involved in subcutaneous and systemic mycoses.[10] The minimum inhibitory concentration (MIC) of terbinafine against *S. schenckii* is 0.11 μg ml^{-1}, indicating significant *in vitro* activity.[11]

Clinical studies and case reports have suggested that terbinafine is safe and effective for the treatment of cutaneous and lymphocutaneous sporotrichosis.[12–17] In these studies, doses up to 500 mg daily for variable durations have been employed with good results. However, the optimum regimen and treatment duration for terbinafine in sporotrichosis has not been precisely defined.

The aim of this randomized, double-blind study was to compare the efficacy and safety of two doses of oral terbinafine (500 and 1000 mg day^{-1}) in the treatment of cutaneous or lymphocutaneous sporotrichosis.

Patients and methods

A multicentre, randomized, double-blind, parallel-group study was performed in patients with *S. schenckii* cutaneous or lymphocutaneous infection. Patients were enrolled at three centres in the USA, two in Brazil, one in Colombia and one in Peru. The study was conducted in accordance with the Helsinki declaration (including amendments) and patients gave informed consent.

Patients

Patients were eligible to enrol for the screening phase if they had clinical signs and symptoms of cutaneous or lymphocutaneous sporotrichosis. Patients were eligible for treatment if they were 13–85 years of age and had histopathological evidence for sporotrichosis (characteristic ovoid/cigar-shaped organisms). After inclusion, patients were then excluded (delayed exclusion) if the samples obtained at screening did not yield *S. schenckii* when cultured, were missing or were positive for a different species.

The exclusion criteria included serum creatinine >2 mg dl^{-1}, liver enzyme elevations more than three times the upper limit of normal (ULN), known human immunodeficiency virus (HIV) infection, concomitant use of rifampin or H_2 blockers, pregnancy and lactation.

Patients were also excluded from the study if they were treated with other systemic antifungals for more than 4 days for the same episode of sporotrichosis, or with any trial therapy 8 weeks prior to the study. Antifungal treatment failures were permitted if positive culture results were obtained after discontinuation of the antifungal and prior to the initiation of the study drug. The use of topical or local antifungals for tinea pedis and mucocutaneous candidosis was permitted.

Study design

Patients who fulfilled the inclusion criteria were randomized to receive double-blind treatment with 500 or 1000 mg day^{-1} oral terbinafine. Patients were instructed to take two tablets in the morning and two tablets in the evening; patients received 250 mg terbinafine tablets in the 1000 mg day^{-1} terbinafine group and 250 mg terbinafine tablets plus identical placebo tablets in the 500 mg day^{-1} group. Dose modification/interruption was permitted.

The treatment duration was variable: terbinafine was administered until 1 month after the resolution of clinical signs and symptoms (cure) or up to a maximum of 6 months (24 weeks). Clinical signs and symptoms and safety parameters were evaluated at inclusion (week 0, i.e. baseline) and at intervals of 2 weeks up to 12 weeks of treatment, then at monthly intervals for up to 24 weeks.

Patients who were cured before 24 weeks of treatment entered directly into the 24-week follow-up phase. Patients who were not cured after 24 weeks of treatment but who had negative cultures entered the follow-up phase. Patients who had positive cultures were excluded in order to allow for alternative therapy. Post-treatment assessments were made at weeks 4, 12 and 24 of follow-up.

The study end-points were assessments at the end of treatment (EOT) and at the end of follow-up (end of study, EOS). If lesions were present at EOT or EOS, mycological testing was repeated.

Specimens were obtained for mycological testing by drainage or biopsy of lesions and cultured in accordance with the guidelines of the Centres for Disease Control.

Study assessments

Efficacy

The primary efficacy end-point was the number of patients cured at EOS. The criterion for cure was the resolution of clinical signs and symptoms (lesions and adenopathy). Therefore, patients were classified as cured if their total lesion size was 0 cm^2 and no adenopathy. Total lesion size was based on the sum of individual lesions (i.e. maximum length × maximum width), including newly occurring lesions.

The secondary efficacy assessments included patients who relapsed, i.e. patients who were considered cured at any time during the study, but who later exhibited signs of infection and an increase in total lesion size.

Safety and tolerability

All AEs (clinical events or test abnormalities) were assessed for severity and relationship to the study drug at each visit. Multiple occurrences of the same AE were only counted once for each patient.

Physical examinations included assessment of the patient's general appearance, skin, neck (including thyroid), head, lungs, heart, lymph nodes, extremities and neurological findings. Vital signs (body weight, sitting blood pressure and radial pulse) and ophthalmological examinations (corrected visual acuity, examination of the cornea, tonometry and indirect fundoscopy) were also performed. Retinal photography was performed at baseline and EOT, depending upon the patient's physical condition.

Laboratory measurements included complete blood count, coagulation tests, serum creatinine, transaminases, γ-glutamyl transferase, alkaline phosphatase, total bilirubin, glucose, electrolytes and urinalysis.

Statistics

Efficacy analyses were performed on the intent-to-treat (ITT) population, which consisted of all random-

ized patients with a positive mycological culture for *S. schenckii* who received at least one dose of the study drug. The primary end-point was clinical cure at EOS and, for patients who prematurely discontinued the study (other than delayed exclusions), the last postbaseline observation was carried forward.

All safety analyses were performed on the safety population, which consisted of all patients who received at least one dose of study drug and who had at least one postbaseline safety assessment.

Treatment groups were compared using a Cochran–Mantel–Haenszel test or a Fisher's exact test. A value of $P < 0.05$ was considered significant.

Results

A total of 63 patients were randomized to receive either 500 mg day^{-1} terbinafine ($n = 28$; 14–73 years of age) or 1000 mg day^{-1} terbinafine ($n = 35$; 14–85 years). The two treatment groups were similar in age and gender distribution, but not for height, weight and lesion size (Table 1). Three patients in the 500 mg day^{-1} terbinafine group were lost to follow-up and one patient withdrew consent. Four patients in the 1000 mg day^{-1} terbinafine group were lost to follow-up and two patients were delayed exclusions.

The mean (±SD) duration of treatment with 500 mg day^{-1} terbinafine was 17.7 ± 5.8 weeks, compared with 13.9 ± 6.7 weeks with 1000 mg day^{-1} terbinafine. The mean study durations were 36.0 ± 8.7 and 35.8 ± 14.0 weeks with 500 and 1000 mg day^{-1} terbinafine, respectively (ITT population).

Efficacy

At EOS, 52% of patients treated with 500 mg day^{-1} and 87% treated with 1000 mg day^{-1} terbinafine were cured (Figure 1). The incidence of cure was dose-dependent throughout the study and significantly higher at EOS with 1000 mg day^{-1} terbinafine than with 500 mg day^{-1} terbinafine ($P = 0.004$) (Table 2). Six patients, in the 500 mg day^{-1} terbinafine group only, discontinued because the treatment was ineffective.

Six of the 19 patients in the 500 mg terbinafine group who were clinically cured during the study showed signs of infection at EOS. There were no cases of relapse with 1000 mg terbinafine (Table 3).

The mean (±SD) reductions in lesion size from baseline at EOT were 6.47 ± 2.7 and 10.75 ± 11.1 cm^2 with 500 and 1000 mg terbinafine, respectively.

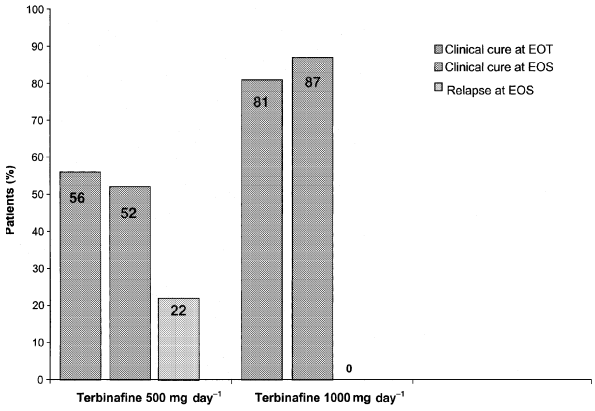

Figure 1 Efficacy of terbinafine in the treatment of sporotrichosis.

Table 1 Baseline demographics and characteristics in the safety population.

	Terbinafine	
	500 mg day^{-1}	1000 mg day^{-1}
	($n = 28$)	($n = 35$)
Mean age [years (range)]	40.7 (14–73)	38.3 (14–85)
Male : female ratio	21 : 7	26 : 9
Weight [mean ± SD (kg)]	59.2 ± 17.4	66.0 ± 12.6* ($n = 34$)
Height [mean ± SD (cm)]	160.0 ± 10.4 ($n = 27$)	164.0 ± 10.3*
Mean lesion size [cm^2 (range)]	17.4 (0.22–117.3)	75.1* (0.63–1571.5)

*$P < 0.05$ vs. 500 mg day^{-1} terbinafine group.

Table 2 The incidence of cure in the ITT population (lesion size = 0 cm^2 and no adenopathy).

	Terbinafine	
	500 mg day^{-1} ($n = 27$) *n* (%)	1000 mg day^{-1} ($n = 34$) *n* (%)
Treatment period		
EOT	15/27 (56)	25/31 (81)*
Post-treatment period		
Postweek 4	12/25 (48)	25/29 (86)**
Postweek 12	9/15 (60)	22/25 (88)
Postweek 24	8/11 (73)	17/20 (85)
EOS	14/27 (52)	27/31[1] (87)**

*$P < 0.05$; **$P < 0.004$ vs. 500 mg day^{-1} terbinafine group.
[1]Three patients were not included at EOS due to missing post-baseline assessment ($n = 2$) and treatment for <2 weeks ($n = 1$).
ITT, intent-to-treat; EOT, end of treatment; EOS, end of study.

Table 3 The occurrence of relapse at EOS.

	Terbinafine	
	500 mg day^{-1} (n = 27) n (%)	1000 mg day^{-1} (n = 34) n (%)
Clinical cure before EOS	19 (70.0)	27 (79.4)
Relapse at EOS[1]	6 (22.0)	0*

*P < 0.005 vs. 500 mg day^{-1} terbinafine group.
[1]Patients who were cured at any time during the study who subsequently exhibited signs of infection.
EOS, end of study.

Table 4 Frequency and nature of adverse events (AEs) in the safety population.

	Terbinafine	
Patients (%) with at least one related AE	500 mg day^{-1} n = 10/28 (35.7%)	1000 mg day^{-1} n = 17/35 (48.6%)
Body as whole – general disorders	5 (17.9)	13 (37.1)
Gastrointestinal system disorders	5 (17.9)	12 (34.3)
Diarrhoea	4 (14.3)	3 (8.6)
Central and peripheral nervous system disorders	4 (14.3)	5 (14.3)
Vision disorders	1 (3.6)	0
Special senses disorders (metallic, bitter taste)	2 (7.1)	6 (17.1)
Liver and biliary system disorders	1 (3.6)	0
Musculoskeletal disorders	0	1 (2.9)
Hearing and vestibular disorders	0	1 (2.9)
Metabolic and nutritional disorders	0	2 (5.7)
Psychiatric disorders	0	1 (2.9)

Safety and tolerability

The majority of AEs were mild or moderate in severity and typical for the class of drug. The most frequently recorded AEs in both treatment groups were related to the gastrointestinal and central nervous systems (Table 4).

One patient (3.6%) in the 500 mg day^{-1} terbinafine group and two patients (5.7%) in the 1000 mg day^{-1} terbinafine group required a dose reduction/interruption. The patient in the 500 mg day^{-1} terbinafine group had their treatment interrupted because of tonsillitis, while one patient in the 1000 mg day^{-1} terbinafine group had their treatment interrupted because of typhoid fever, and one patient due to influenza-like symptoms. None of these AEs were suspected to be related to the study drug.

There were two discontinuations (5.7%) in the 1000 mg day^{-1} terbinafine group because of a drug-related AE: one case of gastrointestinal haemorrhage, which was considered to be serious, and one case of progressive abdominal pain. There were no deaths during the study.

There were no clinically relevant changes in vital signs, but more patients in the 500 mg day^{-1} terbinafine-treated group (21.4%) experienced weight gain, compared with the 1000 mg day^{-1} terbinafine group (6.9%).

The number of patients with newly occurring ophthalmological abnormalities was slightly higher in the 500 mg day^{-1} terbinafine group compared with the 1000 mg day^{-1} terbinafine group (seven and one, respectively), particularly for peripheral retinal abnormalities, but low overall given the presence of pre-existing abnormalities at baseline in both treatment groups.

Both treatment groups had a similar number of newly occurring laboratory abnormalities, and elevations of liver enzymes were recorded intermittently in both treatment groups. The most frequently recorded new laboratory abnormality in both groups was neutropenia: five of 22 (22.7%) and six of 27 (22.2%) with 500 and 1000 mg day^{-1} terbinafine, respectively. In six (54.5%) cases the white blood cell counts (WBC) returned to within normal levels during terbinafine therapy. In the remaining five (45.4%) cases the WBC remained low, returning to normal levels after completion of terbinafine therapy (assessed at follow-up).

Discussion

This randomized study of 63 patients showed that oral terbinafine (500 and 1000 mg day^{-1}) is an effective treatment for cutaneous and lymphocutaneous sporotrichosis. The incidences of cure at EOS were significantly higher with 1000 mg day^{-1} terbinafine, compared with 500 mg day^{-1} terbinafine. Lesions and adenopathy either resolved within 12–24 weeks of treatment in the majority of patients, or there was a reduction in lesion size in patients who were not cured at EOS.

Both doses of terbinafine were generally well-tolerated. Drug-related AEs were mild to moderate, rarely required withdrawal and were consistent with the known tolerability profile of terbinafine. The frequency of drug-related AEs was slightly higher in the 1000 mg day^{-1} treatment group. There were no significant differences in changes in vital signs, ophthalmological examinations and laboratory tests between the 500 and 1000 mg day^{-1} treatment groups.

Mycological susceptibility tests have suggested that terbinafine has potent *in vitro* activity against a range of

fungi that are associated with subcutaneous and systemic mycoses, including *Aspergillus* spp., *Scopulariopsis brevicaulis, Blastomyces dermatitidis* and *Histoplasma capsulatum*.[11,18] Furthermore, clinical evidence has suggested that terbinafine may be effective against diseases such as chromoblastomycosis, fungal mycetoma, aspergillosis, histoplasmosis and cutaneous leishmaniasis.[19,20] The results of this study now provide clinical evidence supporting the use of terbinafine for the treatment of *S. schenckii* sporotrichosis.

New antifungal agents with greater efficacy, improved tolerability and more convenient dosing regimens compared with older and widely used therapies are required for the treatment of deep subcutaneous mycoses. Conventional treatment of cutaneous or lymphocutaneous sporotrichosis with SSKI is still recommended and, indeed, is effective against various mycotic pathogens.[7] Moreover, SSKI is inexpensive, which is an important factor in underdeveloped countries where sporotrichosis is endemic. However, SSKI is inconvenient to take and is associated with side-effects such as a metallic taste, salivary gland enlargement, gastrointestinal intolerance, hyperthyroidism and rash.[6,21,22] Furthermore, SSKI has not been subjected to specific clinical trials.

In addition to SSKI, guidelines suggest that itraconazole may also be used for the treatment of sporotrichosis.[7] Evidence from open clinical trials has shown that itraconazole has demonstrated success rates of ≈90% in the treatment of cutaneous or lymphocutaneous sporotrichosis.[23–25] The results achieved in this double-blind dose-ranging study with terbinafine 1000 mg day^{-1} (87%) is comparable to that with itraconazole. However, the relative efficacy of these two oral antifungals can only be determined in a head-to-head comparative trial.

Therapies that are primarily fungistatic, such as the triazoles, may also be associated with clinical and mycological relapse. For example, in the treatment of superficial dermatophytoses, fungistatic agents show higher rates of relapse compared with terbinafine, which is primarily fungicidal.[9] In this study, there were no cases of relapse with the 1000 mg day^{-1} terbinafine dose. Of the patients who were cured with 500 mg day^{-1} terbinafine, 32.5% (six of 19) exhibited signs of infection within 6 months following treatment.

Terbinafine is highly lipophilic, accumulating in peripheral tissues, particularly those rich in keratin or lipids, at concentrations of 10–1000 times the MIC for many subcutaneous and systemic fungal pathogens. Even with 1 week of daily treatment, terbinafine remains in most skin compartments at high concentrations for 2–3 months after discontinuation.[26,27] This, together with its unique fungicidal mechanism of action, may have accounted for the complete absence of relapse in the 1000 mg day^{-1} terbinafine group.

In conclusion, up to 24 weeks of oral terbinafine treatment is effective for cutaneous or lymphocutaneous sporotrichosis. The cure rates were high with 500 and 1000 mg day^{-1} oral terbinafine, but the response was dose-dependent and significantly greater with the higher dose. There were no cases of relapse with up to 6 months of follow-up in the 1000 mg day^{-1} terbinafine group. The tolerability profile of terbinafine was very good and similar with both the 500 and 1000 mg day^{-1} dose. Therefore, up to 24 weeks of treatment with 1000 mg day^{-1} oral terbinafine should be considered for cutaneous or lymphocutaneous sporotrichosis.

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References

1 Kwon-Chung KJ, Bennet JE. Sporotrichosis. In: Kwon-Chung KJ, Bennett JE (eds), *Medical Mycology*. Philadelphia: Lea & Febiger, 1992: 707–29.
2 Hajjeh R, McDonnell S, Reef S *et al.* Outbreaks of sporotrichosis among tree nursery workers. *J Infect Dis* 1997; **176**: 499–504.
3 Chapman SW, Daniel CR. Cutaneous manifestations of fungal infection. *Infect Dis Clin N Am* 1994; **95**: 879–910.
4 Winn RE. Sporotrichosis. *Infect Dis Clin N Am* 1988; **2**: 899–911.
5 Rex JH, Bennet JE. Administration of potassium iodide to normal volunteers does not increase killing of *Sporothrix schenckii* by their neutrophils or monocytes. *J Med Vet Mycol* 1990; **28**: 185–9.
6 Kauffman CA. Old and new therapies for sporotrichosis. *Clin Infect Dis* 1995; **21**: 981–5.
7 Kauffman CA, Hajjeh R, Chapman SW. Practice guidelines for the management of patients with sporotrichosis. For the Mycoses Study Group. Infectious Diseases Society of America. *Clin Infect Dis* 2000; **30**: 684–7.
8 Evans EGV, Sigurgeirsson B. Double blind, randomised study of continuous terbinafine compared with intermittent itraconazole in the treatment of toenail onychomycosis. *BMJ* 1999; **318**: 1031–5.

9 Sigurgeirsson B, Olafsson JH, Steinsson JB *et al.* Long-term effectiveness of treatment with terbinafine vs itraconazole in onychomycosis: a 5-year blinded prospective follow-up study. *Arch Dermatol* 2002; **138**: 353–7.
10 Ryder NS, Leitner I. *In vitro* activity of terbinafine (Lamisil): an update. *J Dermatol Treat* 1998; **9**: S23–8.
11 Shadomy S, Espinel-Ingroff A, Gebhart RJ. *In-vitro* studies with SF 86–327, a new orally active allylamine derivative. *Sabouradia* 1985; **23**: 125–32.
12 Hull PR, Vismer HF. Treatment of cutaneous sporotrichosis with terbinafine. *Br J Dermatol* 1992; **126**(Suppl. 39): 51–55.
13 Forsana CV, Carrozzo V, Forte I, Peserico A. Cutaneous lymphangitic sporotrichosis treated with terbinafine. *Acta Dermatol Venereol* 1994; **3**: 161–3.
14 Kudoh K, Kamei E, Terunama A *et al.* Successful treatment of cutaneous sporotrichosis with terbinafine. *J Dermatol Treat* 1996; **7**: 33–35.
15 Jacyk WK, Ayerst KF, Röscher M. Sporotrichosis. Review of sixty-five cases from South Africa. *Mikol Lek* 2000; **7**: 189–96.
16 Morishita N, Yamazaki K, Ninomiya J *et al.* A case of lymphocutaneous sporotrichosis. *Nippon Ishinkin Gakkai Zasshi* 2001; **42**: 149–54.
17 Morris-Jones R, Sarkany R, Hay J. Lymphocutaneous sporotrichosis. *Br J Dermatol* 2001; **145**: 38–39.
18 Petranyi G, Meingassner JG, Mieth H. Antifungal activity of allylamine derivative terbinafine *in vitro*. *Antimicrob Agents Chemother* 1987; **31**: 1365–8.
19 Hay RJ. Therapeutic potential of terbinafine in subcutaneous and systemic mycoses. *Br J Dermatol* 1999; **141**: 36–40.
20 Perez A. Terbinafine: broad new spectrum of indications in several subcutaneous and systemic and parasitic diseases. *Mycoses* 1999; **42**(Suppl. 2): 111–4.
21 Lesher JL, Fitch MH, Dunlap DB. Subclinical hypothyroidism during potassium iodide therapy for lymphocutaneous sporotrichosis. *Cutis* 1994; **53**: 128–30.
22 Scully RE, Mark EJ, McNeely WF, McNeely BU. Case records of the Massachusetts General Hospital: case 28, 1994. *N Engl J Med* 1994; **331**: 181–7.
23 Conti Diaz IA, Civilia E, Gezule E *et al.* Treatment of human cutaneous sporotrichosis with itraconazole. *Mycoses* 1992; **35**: 153–6.
24 Sharkey-Mathis PK, Kauffman CA, Graybill JR *et al.* Treatment of sporotrichosis with itraconazole. *Am J Med* 1993; **95**: 279–85.
25 Karakayali G, Lenk N, Ali N, Gungor E, Artuz F. Itraconazole therapy for lymphocutaneous sporotrichosis: a case report and review of the literature. *Cutis* 1998; **61**: 106–7.
26 Faergemann J, Zehender H, Millerioux L. Levels of terbinafine in plasma, stratum corneum, dermis–epidermis (without stratum corneum), sebum, hair and nails during and after 250 mg terbinafine orally once daily for 7 and 14 days. *Clin Exp Dermatol* 1994; **19**: 121–6.
27 Adel-Rhaman SM, Nahata MC. Oral terbinafine: a new antifungal agent. *Ann Pharmacother* 1997; **31**: 445–56.

